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DRUG DISCOVERY

Optimization of a blend of natural and synthetic disintegrants in the formulation of fast disintegration tablets of Salbutamol

Yiobor Ogoh, Sylvester O Eraga, Magnus A Iwuagwu

Department of Pharmaceutics and Pharmaceutical Technology,
Faculty of Pharmacy, University of Benin,
Benin City, 300001, Nigeria

Corresponding author:
Sylvester O Eraga
Department of Pharmaceutics and Pharmaceutical Technology,
Faculty of Pharmacy, University of Benin,
PMB 1154, Benin City, 300001, Nigeria.
Tel: +2348030884928, Email: eragaso@uniben.edu

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ABSTRACT

Fast disintegrating tablets are solid dosage forms that disintegrate rapidly without chewing upon contact with saliva in the oral cavity. The aim of the study was to formulate and evaluate fast disintegrating tablets of salbutamol using an optimized combination of disintegrants of natural and synthetic origin. A Box Behnken model was used to generate possible combinations and

concentrations of *Pleurotus tuber-regium* powder, croscarmellose sodium and microcrystalline cellulose resulting in nine batches. Powder blends of the batches were slugged and broken down into granules. Flow parameters and drug-excipient interaction (Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR)) analyses were carried out on the granules. Compressed tablets were evaluated for weight variation, friability, hardness, disintegration time, dissolution profiles and drug release kinetics. Granules gave Carr's indices, Hausner's ratios and angles of repose values ranging from 33-46 %, 1.51-1.87 and 26-30°, respectively, indicating good flow. Friability of the tablets ranged from 0.02-1.30 % while their hardness values was between 4.04-5.16 kp and disintegration times < 30 sec. Dissolution profiles of the tablets showed over 60% salbutamol release within 5 min with the release most consistent with first order kinetics. DSC and FTIR studies showed no interaction between salbutamol and the formulation excipients. Fast disintegrating tablets of salbutamol with acceptable tablet properties was successfully produced using optimized concentrations of *Pleurotus tuber-regium*, croscarmellose sodium and microcrystalline cellulose. All the formulated tablets disintegrated within 30 sec with satisfactory hardness and dissolution profiles.

Keywords: Salbutamol, disintegrants, *Pleurotus tuber-regium*, FDTs

1. INTRODUCTION

Fast disintegrating tablets (FDTs) are tablets that disintegrate instantaneously when placed on the tongue, releasing the drug that dissolves or disperses in the saliva (Zade *et al*., 2009). These dosage forms are also commonly known as fast melt, quick melt, orally disintegrating or orodispersible tablets and they have the unique property of disintegrating in seconds within the mouth (Agarwal *et al*., 2007).

FDTs are new generation formulations expected to be beneficial to patients having difficulties in swallowing or chewing, leading to better compliance by these patients to dosage regimen with improved treatment outcomes and quality of life (Shirsand *et al*., 2010). The concept of fast dissolving drug delivery system has received increasing interest in the last decade and is becoming a rapidly growing area in the pharmaceutical industry (Narmada *et al*., 2009, Shirsand *et al*., 2009, Biswajit *et al*., 2011, Eraga *et al*., 2014).

Drugs formulated as FDT have the advantage of improved bioavailability as a result of pre-gastric absorption in the mouth and oesophagus as well as a reduced amount of drug undergoing first-pass metabolism. Since the pre-gastric absorption of drugs will necessarily leads to faster onset of action, drugs used in emergency situations or those drugs with short biological half-life and undergo heavy first-pass metabolism are ideal formulation candidates as FDTs.

Various methods have been employed in the formulation of FDTs and one of such methods is the combination of two or more super-disintegrants. Since disintegrants aids tablet breakup when in contact with fluid, a combined system of super-disintegrants (especially if the disintegrants mode of action are different) may act synergistically to effect fast disintegration. *Pleurotus tuber-regium* is a tropical tuber mushroom whose powder is commonly used in Nigeria as a condiment in soup thickening. Its powder has been shown to possess extensive swelling abilities and hence a good disintegrant (Iwuagwu and Onyekweli 2002, Eraga *et al*., 2018).

Salbutamol is a short-acting β2-adrenergic receptor agonist used in the relaxation of the smooth muscles of the airways, hence, it is used in relieving bronchospasm in conditions such as asthma, chronic obstructive pulmonary disease (COPD) and exercise-induced bronchoconstriction (Billington *et al*., 2017). Salbutamol provides rapid relief of acute asthma symptoms by relaxing smooth muscles of the airway and improving airflow. Its effects start in about 10-15 minutes after oral administration with maximum effects within 30 minutes, hence a fast disintegrating salbutamol tablet will result in quick onset of drug action and rapid relief of asthma symptoms.

With the focus on searching for pharmaceutical excipients of natural origin nowadays, this study aims at formulating fast disintegrating tablets of salbutamol using a combination of disintegrants of natural and synthetic origin.

2. MATERIALS AND METHODS

Materials

Salbutamol (SureChem Product Ltd., Suffolk, England), croscarmellose sodium (FMC Corporation, Philadelphia, USA), microcrystalline cellulose (Avicel®) (BDH Chemicals Ltd, Poole, England). Mannitol, magnesium stearate and talc (Edo Pharmaceuticals, Benin City, Edo State, Nigeria). *Pleurotus tuber-regium* tubers were bought from a local market in Benin City, Edo State, Nigeria and processed into powder in our laboratory.

Preparation of *Pleurotus tuber-regium* powder

Using an earlier reported method, dry tubers of *P. tuber-regium* were processed into powder (Iwuagwu and Onyekweli, 2002). The brownish outer layer of the tuber was peeled to expose the whitish inner sclerotia, which was diced and blended into powder using a blending machine. The resulting powder was dried in an oven at 60 °C for 30 min and then passed through a 210 µm laboratory sieve to obtain fine powder.

Preparation of salbutamol powder blends

Experimental design

A preliminary experimental study involving the development of a Box Behnken Design (BBD) using Design Expert® 10.0 (Statease Inc., Minneapolis, U.S.A.) to determine the possible combinations of *Pleurotus tuber-regium* powder, croscarmellose sodium and microcrystalline cellulose for maximizing the disintegration time of the formulated tablets was carried out. The range and levels of the variables (disintegrants) used in the experimental design study are shown in Table 1. The BBD combines the vertices of a hypercube whose coordinates are given by a 2^n factorial design to give 17 possible combinations of the disintegrants (Table 2). Same combinations were treated as a batch and a total of nine (9) batches were selected and used in the formulation of tablets as shown in Table 3.

Table 1: Experimental range and level of the disintegrants

Independent variables (Disintegrants)	Symbol	Coded levels		
		-1	0	+1
		Actual levels (mg)		
Pleurotus tuber-regium	X_1	10	15	20
Croscarmellose sodium	X_2	5.0	7.5	10
Microcrystalline cellulose	X_3	2.0	2.0	2.0

Table 2: Composition of experimental batches of tablets

Batches	Runs	Factors					
		Coded values			Actual values		
		X_1	X_2	X_3	X_1	X_2	X_3
F1	1	0	0	0	15.0	7.5	2.0
	2	0	0	0	15.0	7.5	2.0
	3	0	0	0	15.0	7.5	2.0
	4	0	0	0	15.0	7.5	2.0
	5	0	0	0	15.0	7.5	2.0
F2	6	-1	0	+1	10.0	7.5	2.0
	7	-1	0	-1	10.0	7.5	2.0
F3	8	-1	-1	0	10.0	5.0	2.0
F4	9	+1	-1	0	20.0	5.0	2.0
F5	10	+1	+1	0	20.0	10.0	2.0
F6	11	0	-1	-1	15.0	5.0	2.0
	12	0	-1	+1	15.0	5.0	2.0
F7	13	-1	+1	0	10.0	10.0	2.0
F8	14	0	+1	-1	15.0	10.0	2.0
	15	0	+1	+1	15.0	10.0	2.0
F9	16	+1	0	-1	20.0	7.5	2.0
	17	+1	0	+1	20.0	7.5	2.0

Table 3: Formula for the preparation of the salbutamol powder blends

Ingredients (mg)	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol	4	4	4	4	4	4	4	4	4
Pleurotus tuber-regium	15	10	10	20	20	15	10	15	20
Croscarmellose sodium	7.5	7.5	5	5	10	5	10	10	7.5
Microcrystalline cellulose	2	2	2	2	2	2	2	2	2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	78.5	83.5	86	76	71	81	81	76	73.5

One hundred tablets per batch of the nine (9) batches (F1 - F9) from the preliminary study were formulated by weighing the calculated amounts of salbutamol powder, *Pleurotus tuber-regium* powder, croscarmellose sodium and microcrystalline cellulose into a clean and dry mortar and mixed. The amounts of mannitol were added, thoroughly mixed, and then passed through a 212 µm sieve. The powder blends were compressed into slugs with the aid of a heavy-duty tableting machine (Koln Niehi, Germany). The slugs were broken down into granules using a mortar and pestle and passed through an 850 µm sieve. The calculated amounts of magnesium stearate and talc previously weighed and mixed was then added to the granules in geometric proportion and mixed intimately. The granules were analyzed for their flow properties and drug-excipients compatibility studies.

Flow properties of granules

Bulk and tapped densities

About 1.5 g of granules was poured gently into a 50 ml measuring cylinder and the volume occupied by the granules noted. The ratio of the weight of the granules to the volume occupied was recorded as the bulk density. The measuring cylinder containing the granules was tapped 100 times on a wooden platform and the new volume occupied by the granules was noted and used to calculate the tapped density.

Carr's index

The difference between the tapped and bulk densities of the granules divided by the tapped density was calculated and expressed as a percentage.

Hausner's ratio

The ratio of the tapped density to the bulk density of the granules was calculated and recorded as the Hausner's ratio.

Angle of repose

The fixed funnel method was used to determine the angle of repose. A funnel with an orifice diameter of about 0.8 cm was clamped with its tip 3.0 cm above a white paper placed on a flat horizontal surface. Granules (5 g) were gently poured through the funnel to form a cone-like heap on the white paper. The mean diameter of the base of the cone and the height (h) of the cone were determined and used to calculate the angle of repose (θ) from Equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots\ldots \quad (1)$$

Compatibility studies

Drug-excipients interaction studies were carried out on the batch F5 granules and pure salbutamol powder using DSC and FTIR analyses. The DSC analysis was carried out using the DSC822e Differential Scanning Calorimeter (Netzsch DSC 204F1 Phoenix A apparatus, GmbH, Germany). About 4.0 mg of the sample was weighed into an aluminium pan (sample holder) and sealed. The seal was broken by piercing and the pan placed in the calorimeter previously calibrated with indium and nitrogen as the purge gas. Heating of the sample from 30 to 350 °C was carried out under nitrogen at a rate of 10 °C/min and a flow rate of 70 ml/min. The FTIR analysis was done using a FTIR Spectrophotometer (Spectrum BX, Perkin Elmer, Beaconsfield Bucks, England). Five milligrams of the granules was dry-mixed with potassium bromide (KBr) powder and compressed into a 200 mg weight tablet. The tablet was scanned over a range of 4000 - 1000 cm^{-1} in the spectrophotometer.

Granule compression

Using a single punch tableting machine (F-3 Manesty Machines, UK), the granules were compressed at 30 arbitrary units into tablets. Tablets of uniform weight (110 mg) were compressed using the required weight of granules. Compressed tablets were placed in air tight containers until evaluation.

Tablet evaluations

Weight variation

Twenty (20) tablets were selected at random from each batch and weighed individually using an electronic weighing balance (B154, Teledo Switzerland). The average weight of the tablets and their standard deviation was calculated.

Friability

Pre-weighed tablets (10) were placed in a Roche friabilator (Erweka-ZT4 Heusenstamm, Germany) and rotated at a speed of 25 rpm for 4 minutes. The tablets were dusted and reweighed. The difference between the initial and final tablet weights divided by the initial weight and expressed as a percentage was recorded as the friability of the tablets.

Hardness

The compression force required to break or crack the tablets was determined using an electrically powered tablet hardness tester (Campbell Electronics, Model HT-30/50, India). Five (5) randomly selected tablets from each batch was used for the test and the mean force and standard deviation were recorded.

Disintegration time

The disintegrating time for the various batches of tablets in distilled water was carried out using the BP disintegration apparatus (MK IV, Manesty Machines, UK) maintained at a temperature of 37 ± 0.5 °C. Six (6) tablets were randomly selected from each batch and placed in each of the tube forming the rack assembly of the tester. The assembly was oscillated in an upward and downward motion until complete disintegration of the six tablets without any residue on the mesh at the bottom of the rack assembly. The average time of disintegration and standard deviation was calculated.

In vitro dissolution studies

Dissolution profiles of the salbutamol tablets were carried out using the USP dissolution test apparatus. The apparatus containing 900 ml of phosphate buffer as dissolution fluid was maintained at a temperature of 37 ± 0.5 °C with paddle rotation of 100 rpm. Aliquots (5 ml) were withdrawn at an interval of 5 min for a period of 30 min and filtered (Whatmann No. 1). Aliquots (5 ml) of fresh buffer solution at same temperature was used to replenish the dissolution fluid after each withdrawal. The filtered solutions were diluted and analysed spectrophotometrically at 276 nm and the amount drug dissolved was extrapolated from the equation gotten from the calibration plot of pure salbutamol.

In vitro release kinetics

The data obtained from the dissolution studies were subjected to different models to determine the pattern of drug release. The models included zero order, first order, Higuchi and Korsmeyer-Peppas.

Statistical analysis

Mean and standard deviations of replicate determinations was computed and reported. Student's t-test at 5 % level of significance was used to analyze the statistical differences in the tablet and granules parameters of the different batches using GraphPad InStat 3.10.

3. RESULTS

Flow properties of salbutamol granules

Table 4 shows the bulk and flow properties of the various batches of the salbutamol granules prepared from their powder blends. Their bulk and tapped densities values were between 0.21 - 32 mg/ml and 0.45 - 0.49 mg/ml, respectively. The Carr's indices and Hausner's ratios were between 33.80 - 46.32 % and 1.51 - 1.87, respectively, indicating that the powder blends had fair to poor flow

characteristics. There were significant differences ($p < 0.05$) among the Carr's indices values of the granules. The angles of repose were between 26.04 - 30.03° which indicated that the powder blends had good flow properties.

Table 4: Pre-compression parameters of the various batches of salbutamol granules

Batches	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F1	0.32 ± 0.013	0.48 ± 0.002	33.80 ± 2.48	1.51 ± 0.06	27.30 ± 0.56
F2	0.27 ± 0.014	0.46 ± 0.003	40.75 ± 3.08	1.69 ± 0.09	26.48 ± 0.98
F3	0.29 ± 0.003	0.49 ± 0.014	39.46 ± 3.03	1.65 ± 0.08	28.34 ± 1.15
F4	0.31 ± 0.002	0.48 ± 0.003	36.47 ± 0.31	1.57 ± 0.07	30.03 ± 0.32
F5	0.25 ± 0.001	0.47 ± 0.006	46.32 ± 0.68	1.87 ± 0.02	26.04 ± 1.21
F6	0.27 ± 0.011	0.48 ± 0.009	44.44 ± 1.07	1.80 ± 0.04	27.82 ± 1.10
F7	0.28 ± 0.009	0.48 ± 0.002	41.66 ± 1.92	1.72 ± 0.06	28.35 ± 2.89
F8	0.26 ± 0.011	0.45 ± 0.010	46.06 ± 1.24	1.85 ± 0.04	27.54 ± 1.88
F9	0.32 ± 0.005	0.49 ± 0.005	34.98 ± 1.47	1.54 ± 0.03	29.90 ± 0.39

All readings were taken in triplicate ± standard deviation.

Drug-excipients compatibility studies

DSC analysis

Figure 1 (a) and (b) show the DSC thermograms of pure salbutamol powder and its granules respectively. The pure salbutamol thermogram showed a distinct sharp endothermic trough at 160 °C which corresponds to the melting point of the amorphous salbutamol powder. The thermogram of the granules showed the characteristic trough seen in the pure salbutamol hence the absence of new troughs or shifts in the patterns indicates the absence of chemical interaction in the powder mixing and slugging processes.

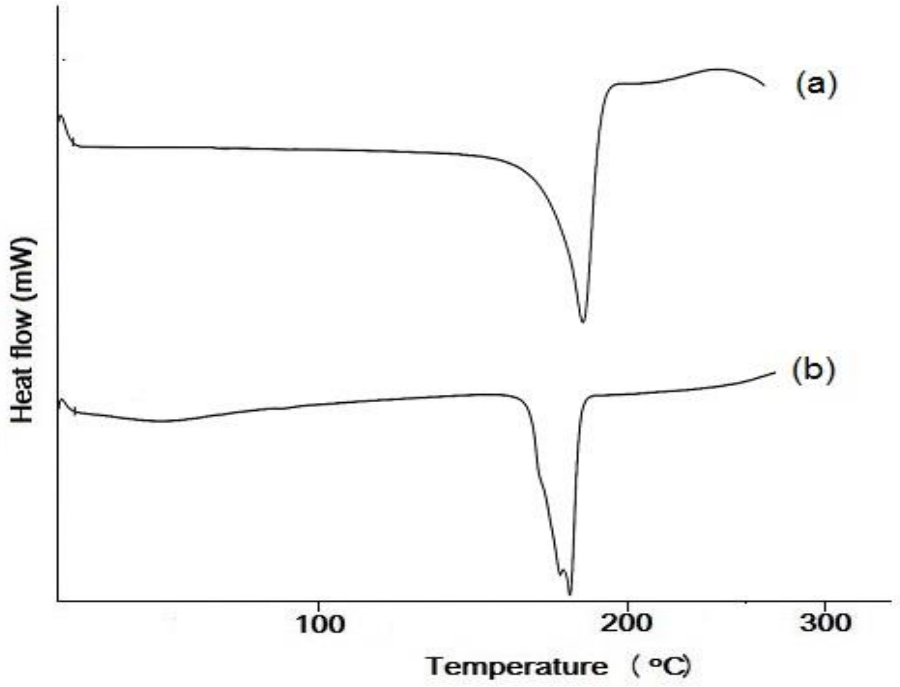

Figure 1: DSC spectra of pure salbutamol (a) and the formulated granules (b) of the powder blend

FTIR analysis

FTIR spectrum of pure salbutamol showed characteristic absorption bands at 3600, 2100, 1600 and 1000 cm^{-1} (Figure 2 (a)). These bands noted for salbutamol did not change when compared with the spectrum of the granules (Figure 2 (b)). The absence of any

shift in the FTIR bands suggests the absence of chemical interaction and complex formation between salbutamol and excipients during the process of mixing and slugging.

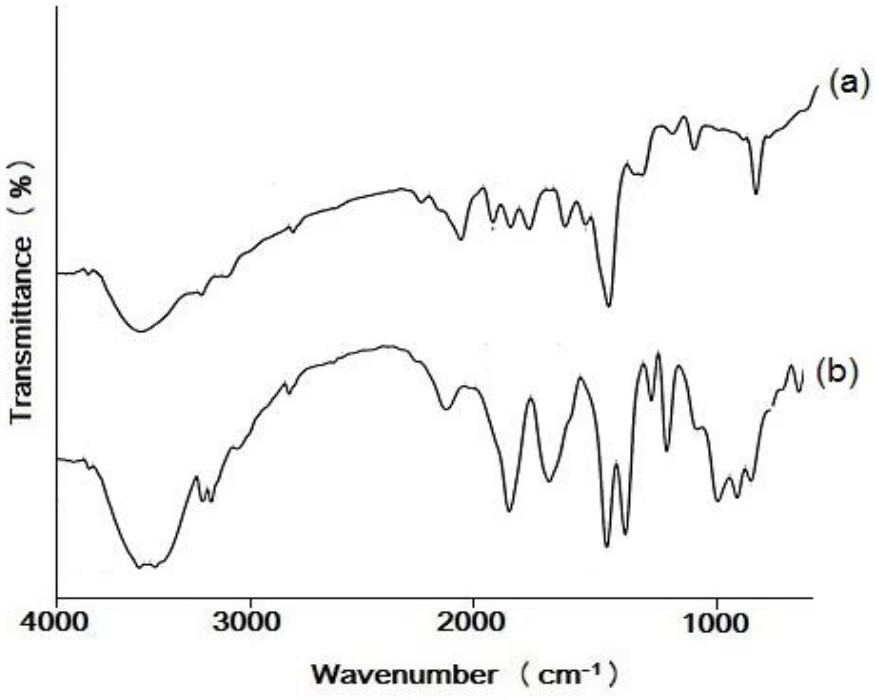

Figure 2: FTIR spectra of pure salbutamol (a) and the formulated granules (b) of the powder blend

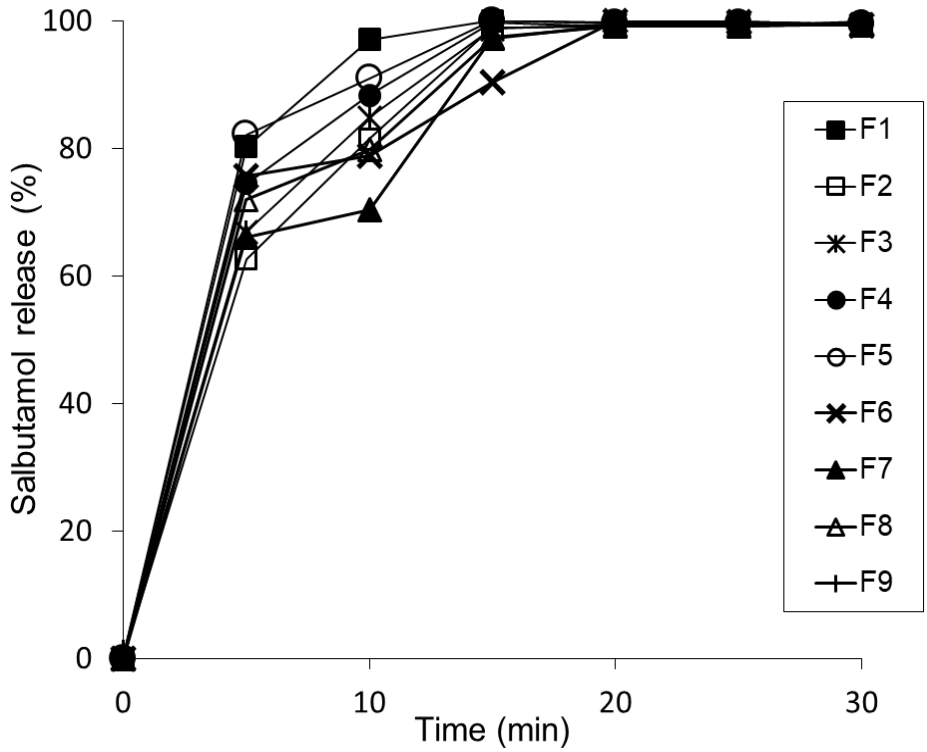

Figure 3: Dissolution profiles of the different batches of the formulated salbutamol tablets (F1-F9)

Tablet properties

Table 5 shows some post compression parameters of the diffeent batches of the formulated salbutamol tablets. The average weights of the prepared tablets were between 105.9 - 108.0 mg while their hardness values were between 4.04 - 5.16 kp suggesting tablets of average hardness. The percentage friability of all the batches of tablets was less than 1.0 % except for batches F1 and F8 with 1.30 and 1.06 % respectively.

All the tablets disintegrated within 30 sec with the F6 batch of tablets showing the lowest time of 19.33 sec and the F3 tablets with the highest time of 26.0 sec. The result from the dissolution profiling of all the batches of salbutamol tablets is shown in Figure 3. The tablets showed comparable release profiles with over 60 % of drug released within 5 min and 100 % within 20 min while the release kinetics (Table 6) of the drug from the salbutamol tablets showed that the drug release fitted more with the first order release model.

Table 5: Physicotechnical properties of salbutamol tablet formulations

Batches	Weight (mg)	Hardness (kp)	Friability (%)	Disintegration time (sec)
F1	108.0 ± 2.98	4.04 ± 0.68	1.30 ± 0.39	21.00 ± 2.65
F2	107.2 ± 1.23	5.16 ± 0.65	0.83 ± 0.15	24.33 ± 2.08
F3	105.9 ± 2.42	5.14 ± 0.22	0.75 ± 0.13	26.00 ± 2.00
F4	106.0 ± 1.17	4.26 ± 0.34	0.87 ± 0.52	21.33 ± 1.15
F5	107.1 ± 1.52	4.26 ± 1.07	0.02 ± 0.01	21.67 ± 1.53
F6	106.3 ± 1.34	4.48 ± 0.33	0.80 ± 0.12	19.33 ± 2.52
F7	106.3 ± 1.25	4.70 ± 0.27	0.66 ± 0.20	25.00 ± 2.00
F8	106.3 ± 1.34	4.66 ± 0.42	1.06 ± 0.35	26.33 ± 2.52
F9	106.0 ± 0.94	4.40 ± 0.31	0.76 ± 0.56	22.33 ± 0.58

All readings were taken in triplicate ± standard deviation.

Table 6: Regression coefficient (R^2) values for the different release models

Batches	Correlation coefficient (R^2)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas (n)
F1	0.4821	0.9989	0.7827	0.6570 (0.118)
F2	0.6448	0.9826	0.8985	0.8696 (0.269)
F3	0.6103	0.9867	0.8788	0.8638 (0.229)
F4	0.5692	0.9963	0.8516	0.8389 (0.191)
F5	0.5186	0.9387	0.8119	0.8708 (0.128)
F6	0.6101	0.8874	0.8715	0.8703 (0.179)
F7	0,6671	0.8270	0.9004	0.7973 (0.277)
F8	0.6328	0.8540	0.8861	0.9014 (0.195)
F9	0.5836	0.8337	0.8559	0.8131 (0.181)

4. DISCUSSION

Fast disintegrating tablets of salbutamol have been formulated and evaluated for their granule and post compression parameters. The prepared salbutamol granules exhibited bulked and tapped densities values suggesting a porous granule system with wide particle size distribution and the tapping of the granules would have resulted in filling of voids by the smaller fine particles. However, their calculated Carr's indices and Hausner's ratios showed granules of fair flow while their angles of repose revealed granules of excellent flow properties. This discrepancy in the flowability of the granules arising from the Carr's indices and Hausner's ratios with the angles of repose can be attributed to the earlier hypothesis of a porous granule system with wide particle size distribution. Since the tapped density test of the granules allowed consolidation of the granules in the measuring cylinder by the tapping process leading to the filling of voids by finer granule particles, thus giving the appearance of a cohesive granule system. Hence the calculated Carr's indices and Hausner's ratios will reflect granules with poor flowability while on the other hand, the angle of repose test that allowed granules free fall with no consolidation reflected non-cohesive, free flowing granules.

The formulated tablets showed minimal weight variation with all the tablets weight variations within the BP acceptable limits of a maximum deviation of ±7.5 % from the average tablet weight (BP, 2009). The good flow of granules leading to uniform die filling has been attributed to minimal tablet weight variations or tablet weight uniformity as this is also significant in contributing to the uniformity of tablets drug content. Also, though the tablet's hardness was of average value, they seem to meet the official compendial specifications as hardness values ranging from 5.0 - 8.0 kp have been recommended as optimum hardness values (BP, 2009), although a lower limit of 4.0 kp has been suggested as also satisfactory (Rudnic and Schwartz, 2006).

The salbutamol tablets also exhibited friability values within recommended specifications except two batches of tablets. Though these tablets did not meet the BP recommendation of 0.8 - 1.0 % friability for uncoated tablets (BP, 2009), however, the European Pharmacopeia makes some allowance up to 2.0 % for tablets prepared by direct compression (EP, 2005). Since a tablets' friability and hardness determines its mechanical strength, it is crucial that FDTs possess sufficient mechanical strength to withstand the stress of handling and transportation while at the same time, not affecting the disintegration times and dissolution properties of the tablet adversely.

The disintegration times of all the tablets met the European Pharmacopeia specification for FDTs of less than 3 min (EP, 2008). As FDTs are expected to be used in emergency situations where quick drug action is desired, the faster the disintegration step, the quicker the dissolution and absorption of the drug into systemic circulation and onset of drug action. This assumption is premise on the fact that the disintegration time and the disintegration process are the limiting steps in the drug dissolution process.

As a fast-disintegrated tablet would necessarily lead to a fast drug dissolution, the dissolution profiles of the tablets can be said to follow the disintegration-dissolution theory that states that, the faster the disintegration of the tablet, the earlier the onset of drug dissolution. With over 60 % of drug release in the first 5 min of dissolution testing, it is expected that such tablet should begin to exact its effects within this time frame.

5. CONCLUSION

Fast disintegrating tablets of salbutamol with acceptable tablet properties was successfully produced using optimized concentrations of *Pleurotus tuber-regium*, croscarmellose sodium and microcrystalline cellulose. All the formulated tablets disintegrated within 30 sec with hardness values above 4 kp and over 60 % of drug released within 5 min.

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Authors' Contribution

MAI designed the study, YO performed the laboratory experiments while SOE prepared the manuscript for publication.

Competing Interest

There are no conflicts of interest in the study.

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Peer-review:

External peer-review was done through double-blind method.

Data and materials availability:

All data associated with this study are present in the paper.

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